American Journal of
EPIDEMIOLOGY

Volume 161

Number 7

April 1, 2005

Sponsored by the Society for Epidemiologic Research
Published by Oxford University Press

ORIGINAL CONTRIBUTIONS

Uterine Cancer after Use of Clomiphene Citrate to Induce Ovulation

Michelle D. Althuis[1], Kamran S. Moghissi[2], Carolyn L. Westhoff[3], Bert Scoccia[4], Emmet J. Lamb[5], Jay H. Lubin[1], and Louise A. Brinton[1]

[1] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.
[2] Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI.
[3] Department of Obstetrics and Gynecology, Columbia University, New York, NY.
[4] Department of Obstetrics and Gynecology, University of Illinois, Chicago, IL.
[5] Department of Obstetrics and Gynecology, Stanford University, Stanford, CA.

Received for publication July 9, 2004; accepted for publication November 8, 2004.

Clomiphene citrate, a selective estrogen receptor modulator, increases estradiol levels and consequently may increase risk of cancer of the uterine corpus. The authors conducted a retrospective cohort study of 8,431 US women (145,876 woman-years) evaluated for infertility during 1965–1988. Through 1999, 39 uterine cancers were ascertained by questionnaire or cancer and death registries. Poisson regression estimated adjusted rate ratios. Study results suggest that clomiphene may increase uterine cancer risk (rate ratio (RR) = 1.79, 95% confidence interval (CI): 0.9, 3.4) and present evidence of a dose response ($p_{trend} = 0.07$) and latency effect ($p_{trend} = 0.04$). Uterine cancer risk increased with clomiphene dose (RR = 1.93, 95% CI: 0.9, 4.0 for >900 mg), menstrual cycles of use (RR = 2.16, 95% CI: 0.9, 5.2 for ≥6 cycles), and time elapsed since initial use (RR = 2.50, 95% CI: 0.9, 7.2 for women followed for ≥20 years). Risk was more strongly associated with clomiphene among nulligravid (RR = 3.49, 95% CI: 1.3, 9.3) and obese (RR = 6.02, 95% CI: 1.2, 30.0) women, with risk substantially elevated among women who were both obese and nulligravid (RR = 12.52, 95% CI: 1.5, 108.0). Clomiphene may increase uterine cancer risk, with higher doses leading to higher risk. Long-term follow-up of infertility cohorts is necessary to clarify the association between clomiphene use and uterine cancer.

clomiphene; fertility agents; gonadotropins; infertility; ovulation; uterine neoplasms

Abbreviations: CI, confidence interval; RR, rate ratio; SIR, standardized incidence ratio.

Unopposed estrogen replacement therapy (1) and tamoxifen (2, 3) increase the risk of endometrial cancer. Ovulation-stimulating agents, including the selective estrogen receptor modulator clomiphene citrate, increase serum estradiol levels during the follicular phase of menstrual cycles of induced ovulation and therefore may also increase uterine cancer risk (4). However, few studies have assessed a link between infertility drugs and uterine carcinoma. In

Correspondence to Dr. Michelle D. Althuis, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, Room 7084, Bethesda, MD 20892-7234 (e-mail: m.althuis@verizon.net).

one study of infertile Israeli women, where 21 uterine cancers were diagnosed during an average of more than 20 years of follow-up, ever compared with never use of ovulation-stimulating agents was associated with approximately a twofold nonsignificant increase in uterine cancer risk (5, 6). In contrast, other cohort studies found no excess uterine cancer risk associated with fertility drug use, but these studies had a short follow-up (less than 10 years) and few cases of uterine cancer (between two and 12) (7–10).

To assess further the effects of ovulation-stimulating drugs, we conducted a large, retrospective cohort study of women treated for infertility in the United States. We followed subjects for nearly 20 years on average and identified 39 uterine cancers. We report here the risk of developing uterine cancer in this cohort of women evaluated for infertility.

MATERIALS AND METHODS

Subjects and follow-up

Brinton et al. (11) previously described this retrospective cohort study, which was conducted at five large reproductive endocrinology and fertility practices in the following metropolitan areas: Boston, Massachusetts; New York City, New York; Chicago, Illinois; Detroit, Michigan; and the San Francisco Bay Area, California. The institutional review boards at the collaborating centers as well as at the National Cancer Institute approved the study protocol. Briefly, eligible patients were evaluated for infertility between 1965 and 1988. Patients evaluated for primary or secondary infertility were eligible for the study, while those who were evaluated for reversal of a tubal ligation were not. Medical records for 12,193 eligible women were abstracted for information to determine the cause of infertility, medications prescribed, menstrual and reproductive histories, and other factors that might affect health status.

A total of 9,751 (80.0 percent) of the patients were successfully traced by using several sources, including clinic records, telephone directories, credit bureaus, postmasters, motor vehicle administration records, and the National Death Index. A total of 1,319 of the eligible women (10.8 percent) chose not to participate in the study. For these women, we retained in the analysis only calendar year, age at study entry, and race.

We mailed questionnaires to patients beginning in 1998, with telephone follow-up attempted for nonrespondents. A total of 5,597 of the patients completed the questionnaire, which ascertained information on sociodemographic factors; updated health status; and lifestyle factors, including menstrual, pregnancy, and breastfeeding history, use of exogenous hormones, and anthropometric factors. We identified 272 patients as deceased. For the patients traced as alive, clinic records, completed questionnaires, and cancer registries provided information on the development of cancers. For patients for whom we were unable to obtain questionnaire data, we had accurate location information that enabled tracing through clinic records ($n = 216$) or cancer registries ($n = 2{,}347$). We attempted to medically verify cancers reported in the questionnaires by obtaining discharge summaries, operative reports, and pathology reports from the institutions at which the diseases had been diagnosed and/or treated. We found two self-reported cancers of the uterine corpus that medical record review subsequently found to be benign.

Statistical analyses

Person-years of accrual began 1 year after clinic registration and continued through the earliest date of cancer diagnosis, death or date last known alive and free of cancer, or December 31, 1999, leading to a total of 155,658 person-years and a median of 18.8 years of follow-up. Thus, patients lost to follow-up after their initial clinic visit, those who denied permission for access to their records, and one woman diagnosed with uterine cancer within 1 year of registration did not fulfill the entry criteria and were excluded, leaving 8,431 analytic study subjects. Pearson's chi-square test and Student's *t* test were used to compare subjects included and excluded from analysis of the three available characteristics: calendar year of study entry, age at first clinic visit, and race. Of the 39 women in the analytic cohort found to have uterine cancer (*International Classification of Diseases for Oncology* code 182), medical or cancer registry records confirmed 23 (19 adenocarcinoma, one clear cell, one papillary, one papillary serous, and one of unknown histology), and death certificates identified four cases. The remaining 12 cases were reported via questionnaires.

We used two analytic approaches to assess cancer risk among the cohort members. We first calculated standardized incidence ratios and 95 percent confidence intervals comparing cancer rates for infertile women with those for US women. Standardized incidence ratios were computed as the number of observed cancer events divided by the expected number of events based on age, race, and calendar-year-specific incidence disease rates for females from cancer registry rates available through the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Thus, for calculated standardized incidence ratios, we used national uterine cancer rates rather than rates in the geographic areas of the study centers. Because both uterine cancer rates and hysterectomy prevalence vary geographically, we undertook another analytic approach that would better control for these factors.

The second analytic approach involved analyses within the cohort of infertile women, which allowed multivariable adjustment for potential confounding factors. For this analysis, person-years were truncated at the time of hysterectomy (self-report via questionnaire); 30 women who had had a hysterectomy within 1 year of their first clinic visit were not eligible for analysis. Thus, the internal comparison comprised 8,401 study subjects for analysis (145,876 person-years). Rate ratios and their 95 percent confidence intervals for developing uterine cancer associated with administration of ovulation-stimulating drugs (ever use, total dosage, cycles prescribed, interval since first use) compared with those for nonusers of these drugs were estimated by Poisson regression using standard methods

TABLE 1. Standardized incidence ratios* comparing uterine cancer risk for infertile women to that for the general population, United States, 1965–1988

	No. of women-years of follow-up	Uterine cancers (no.)		SIR†	95% CI†
		Observed	Expected		
All subjects	155,658	39	24.9	1.56	1.1, 2.1
Clomiphene use					
No	96,975	20	16.0	1.24	0.8, 1.9
Yes	58,683	19	8.9	2.14	1.3, 3.3
p value				0.09	
Dosage (mg)					
1–900	20,463	6	3.1	1.91	0.7, 4.2
>900	38,220	13	5.8	2.26	1.2, 3.9
p_{trend}				0.09	
No. of cycles					
<6	38,071	12	5.9	2.05	1.1, 3.6
≥6	20,612	7	3.0	2.30	0.9, 4.8
p_{trend}				0.11	
Gonadotropins use					
No	140,638	36	22.6	1.60	1.1, 2.2
Yes	15,020	3	2.4	1.26	0.3, 3.7
p value				0.69	

* Computed as the number of observed cancer events divided by the expected number of events based on age, race, and calendar-year-specific incidence disease rates for women from cancer registry rates available through the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.

† SIR, standardized incidence ratio; CI, confidence interval.

(12). For all analyses, the rate ratios were adjusted for study site, age at follow-up (<40, 40–49, ≥50 years), and calendar year of follow-up (prior to 1980, 1980–1989, 1990 or later). Other factors, such as distinct causes of infertility (including anovulation, which was defined primarily by a history of abnormal menses as discussed previously (11)), as well as gravidity, parity, body mass at entry, and hormone replacement therapy use, were included in the regression models to evaluate their roles as potential confounding or modifying factors.

RESULTS

Subjects included in the analysis

The median calendar year at study entry (first clinic visit) was 1978, and the median age of the study subjects at first evaluation was 30 years. Nearly 80 percent of the subjects were known to be Caucasian, and 43 percent had been evaluated for primary infertility. A total of 3,280 (39 percent) of the study subjects were prescribed clomiphene to treat their infertility; 867 (10 percent) received gonadotropins. Subjects included in the analyses and those excluded were not significantly different according to calendar year and age at first evaluation; however, for a larger proportion of the subjects excluded from analysis, information on race was missing (30 percent vs. 11 percent) (11).

Standardized incidence ratios analysis of uterine cancer

Infertile study subjects had a significantly higher risk of developing uterine cancer than women in the general population (standardized incidence ratio (SIR) = 1.56, 95 percent confidence interval (CI): 1.1, 2.1) (table 1). The elevation in uterine cancer risk was more pronounced among clomiphene-exposed women (SIR = 2.14, 95 percent CI:1.3, 3.3) and increased slightly with dose. Risk for women not exposed to clomiphene was similar to that for the general population, with a standardized incidence ratio of 1.24 (95 percent CI: 0.8, 1.9). Although we were limited by the very few women diagnosed with uterine cancers who used gonadotropins ($n = 3$), we found no evidence of higher risk for those exposed (SIR = 1.26, 95 percent CI: 0.3, 3.7) compared with those unexposed (SIR = 1.60, 95 percent CI: 1.1, 2.2).

Internal analyses of uterine cancer risk

The remaining analyses presented in this paper are comparisons within the cohort of infertile women. Most previously established risk factors for uterine cancer demonstrated the expected relation in this cohort (table 2), with the exception of oral contraceptive use, which was in the opposite direction of the expected risk (13). Risk was

TABLE 2. Risk factors for uterine cancer in infertile women,* United States, 1965–1988

Risk factor	Uterine cancer (no.) ($n = 39$)	No. of woman-years of follow-up (total = 145,876)	RR†	95% CI†
Body mass index at first clinic visit (kg/m^2)				
<30	22	108,947	1.00	Reference
≥30	8	6,803	6.32	2.8, 14.3
Missing	9	30,126		
Hormone replacement therapy use				
Never	10	45,097	1.00	Reference
Estrogen only	8	10,364	3.66	1.4, 9.3
Estrogen + progestin	5	27,332	0.60	0.2, 1.8
Unknown	16	63,083	0.90	0.4, 2.6
Anovulatory disorder (cause of infertility)				
No	26	104,687	1.00	Reference
Yes	13	41,189	1.39	0.7, 2.7
Age at menarche (years)				
≤11	9	29,033	1.00	Reference
12	14	39,560	1.16	0.5, 2.7
≥13	13	73,933	0.56	0.2, 1.3
Missing	3	3,350		
Gravidity at study entry				
Nulligravid	20	62,149	1.00	Reference
Gravid	19	83,727	0.68	0.4, 1.3
Parity at follow-up				
Nulliparous	10	33,253	1.00	Reference
Parous	18	80,184	0.76	0.4, 1.7
No. of full-term births				
1	6	21,787	0.74	0.3, 2.0
≥2	6	39,921	0.45	0.2, 1.2
Parous, no. of births unknown	6	18,476	0.75	0.3, 2.1
Parity unknown at follow-up	11	32,440	1.02	0.4, 2.4
Oral contraceptive use				
Never	3	16,624	1.00	Reference
Ever	25	94,632	1.71	0.5, 5.7
Unknown	11	34,620		

* Models were adjusted for calendar year, age, and study site. Inclusion of other variables shown in table 1 in the model did not appreciably change the risk estimates.

† RR, rate ratio; CI, confidence interval.

increased for obese women (body mass index (weight (kg)/height (m)^2) ≥30 vs. <30: rate ratio (RR) = 6.32) and users of estrogen-only hormone replacement therapy (vs. never users: RR = 3.66). Women with an anovulatory disorder also were at elevated risk of uterine cancer (RR = 1.39), an association restricted to women nulligravid at study entry (RR = 2.0, 95 percent CI: 0.8, 5.1). Lower risks of uterine cancer were associated with later age at menarche (≥13 vs. ≤11 years: RR = 0.56), conception prior to the first clinic visit (vs. nulligravidity: RR = 0.68), and higher parity at follow-up (two or more vs. no births: RR = 0.45). Oral contraceptive use was associated with a nonsignificantly increased uterine cancer risk (RR = 1.71, 95 percent CI: 0.5, 5.7). Other causes of infertility such as endometriosis, tubal disease, and male factor, uterine, or cervical disorders were not related to uterine cancer risk (data not shown).

Table 3 presents adjusted risks associated with clomiphene use for infertile women. Clomiphene increased uterine cancer risk twofold (RR = 1.79); however, the rate ratios did not reach the traditional level of significance ($p = 0.09$). Uterine cancer risk increased monotonically with dose ($p_{trend} = 0.07$) and menstrual cycles of use ($p_{trend} = 0.06$), with rate ratios of 1.93 for more than 900 mg and 2.16 for six or more cycles of use, respectively. Number of years

TABLE 3. Clomiphene use and risk of uterine cancer among infertile women, United States, 1965–1988

Clomiphene use	Uterine cancer (no.) ($n = 39$)	No. of women-years of follow-up (total = 145,876)	RR*,†	RR‡	95% CI*
Never	20	90,415	1.00	1.00	Reference
Ever	19	55,461	1.76	1.79	0.9, 3.4
Dosage (mg)					
1–900	6	19,311	1.51	1.56	0.6, 3.9
>900	13	36,150	1.92	1.93	0.9, 4.0
p_{trend}					0.07
No. of cycles					
<6	12	35,859	1.63	1.63	0.8, 3.4
≥6	7	19,602	2.06	2.16	0.9, 5.2
p_{trend}					0.06
No. of years since first use					
<10	5	25,947	1.67	1.68	0.6, 4.9
10–19	9	21,098	1.73	1.80	0.8, 4.1
≥20	5	4,332	2.52	2.50	0.9, 7.2
p_{trend}					0.04

* RR, rate ratio; CI, confidence interval.

† Models were adjusted for calendar year, age, and study site.

‡ Models were additionally adjusted for gravidity at study entry, body mass index, and hormone replacement therapy use.

elapsed since initial clomiphene use was associated with an increased uterine cancer risk ($p_{trend} = 0.04$), with a 2.5-fold increase in risk for women followed for 20 or more years relative to never users. The models of these data were particularly robust, with little difference in risk estimates for the minimally adjusted model (study site, attained age, and calendar time) or more fully adjusted models that included gravidity at entry, body mass index, and hormone replacement use. Our findings were similar when we restricted our analyses to women with medically validated cancers ($n = 27$), yielding a rate ratio of 1.60 (95 percent CI: 0.7, 3.5) associated with ever compared with never use of clomiphene after adjusting for study site, attained age, and calendar time.

Disentangling whether the observed positive association was caused by underlying indications for clomiphene use is complex. Clomiphene is the first line of treatment for women with anovulation disorders, a condition often exacerbated by obesity. Indeed, in this cohort, clomiphene use was more frequent among women with anovulatory disorders (38 percent) than those without (21 percent), and those with anovulatory disorders tended to receive higher cumulative doses ($p_{trend} < 0.01$). Likewise, clomiphene use differed among obese (44 percent) and nonobese (39 percent) women, with obese women receiving higher cumulative doses of clomiphene ($p_{trend} < 0.01$). In contrast, although women nulligravid at entry (41 percent) were more likely to use clomiphene than those who were gravid (36 percent), no differential was evident by dose. Nonetheless, adjustment for these three factors in the multivariable models shown in table 3 demonstrated little effect on the risk estimate, suggesting that clomiphene use is likely an independent predictor of uterine cancer.

Although limited by small numbers of events, we assessed whether clomiphene use predisposed certain women to a higher risk of uterine cancer. Stratified analyses shown in table 4 revealed that the risk of uterine cancer was most strongly associated with clomiphene use for nulligravid (RR = 3.49) and obese (RR = 6.02) women, although neither interaction term was significant. Uterine cancer risk was substantially elevated for the small subgroup of women who were both obese and nulligravid at study entry (RR = 12.52, 95 percent CI: 1.5, 108.0, based on five cases who were exposed to clomiphene) (data not shown). Clomiphene seemed to elevate risk for only those women without anovulatory disorders (RR = 2.22). The relation between clomiphene use and uterine cancer was not modified by parity at follow-up, attained age, or hormone replacement therapy use, although it was based on small numbers in each subgroup.

Since small doses of exogenous estrogens, predominately ethinyl estradiol, have been occasionally prescribed to women using clomiphene, we explored whether the relation between clomiphene and uterine cancer risk could be explained by estrogen use during infertility treatment. Only two women diagnosed with uterine cancer ever used exogenous estrogens. We found similar estimates of uterine cancer risk associated with clomiphene (RR = 1.85) after excluding from analysis those women prescribed estrogen.

Analysis of the relation between gonadotropin use and uterine cancer risk was limited by the small number of users. Only three women with uterine cancer had used

TABLE 4. Modification, by other risk factors, of the risk of uterine cancer associated with clomiphene use,* United States, 1965–1988

	Clomiphene use: ever vs. never				
	Uterine cancers (no.)		RR†	95% CI†	$p_{interaction}$
	Exposed	Unexposed			
Gravidity at entry					
Nulligravid	12	8	3.49	1.3, 9.3	0.08
Gravid	7	12	1.01	0.4, 2.6	
Body mass index at first clinic visit (kg/m^2)					
<30.0	9	13	1.22	0.5, 2.9	0.12
≥30	6	2	6.02	1.2, 30.4	
Unknown	4	5			
Anovulatory disorder					
No	13	13	2.22	1.0, 4.9	0.18
Yes	6	7	0.89	0.3, 2.8	
Gravidity at follow-up					
Nulligravid	4	4	1.67	0.4, 7.3	>0.50
Gravid	9	13	1.23	0.5, 2.9	
Unknown	6	3			
Reproductive status at follow-up					
Nulliparous	5	5	1.54	0.4, 5.5	0.44
Parous	7	11	1.64	0.4, 2.8	
Unknown	7	4			
Attained age (years)					
<40	5	4	2.39	0.6, 9.2	0.47
40–49	7	7	1.54	0.5, 4.5	
≥50	7	9	1.68	0.6, 4.6	
Hormone replacement therapy use					
Never	4	6	0.86	0.2, 3.1	0.50
Estrogen only	4	4	1.33	0.3, 5.5	
Estrogen + progestin	1	4	0.45	0.1, 4.1	
Unknown	10	6			

* Models were adjusted for attained age, calendar time, and study site.
† RR, rate ratio; CI, confidence interval.

gonadotropins previously, resulting in a rate ratio for uterine cancer of 0.70 (95 percent CI: 0.2, 2.3) for exposed compared with unexposed women after we adjusted for calendar year, age, site, body mass index, gravidity at entry, and hormone replacement therapy (data not shown).

Because the retrospective nature of this study resulted in our inability to include the complete cohort for analyses, we also conducted a number of analyses to define the impact of study losses. Since we were unable to obtain completed questionnaires from many of the study subjects, we assessed the uterine cancer risk associated with clomiphene when we restricted our analyses to women for whom questionnaire data were available, yielding a rate ratio of 1.60 (95 percent CI: 0.8, 3.2). Additionally, for those without questionnaire data, we had to rely on identifying cancer outcomes through cancer registry linkages. However, if the last known address was incorrect, we might have missed the true identification of cancer cases among these subjects and incorrectly assigned person-years until the end of the study. We conducted alternative analyses in which we limited the analysis to patients who completed questionnaires or for whom a definite diagnosis of uterine cancer was confirmed by medical records, cancer registries, or death registries. Although the number of person-years decreased, the rate ratios associated with drug exposures changed little, with a rate ratio for clomiphene use of 1.87 (95 percent CI: 1.0, 3.6).

DISCUSSION

Few epidemiologic studies have assessed the risk of uterine cancer associated with infertility treatments among infertile women, in large part because of the rarity of the disease. In our study with approximately 150,000

women-years of follow-up, only 39 uterine cancers were diagnosed. Infertile women were at higher risk of uterine cancer compared with the general population (SIR = 1.56). We found that uterine cancer risk was elevated among clomiphene-treated women (SIR = 2.14), with risk among untreated women similar to that in the general population (SIR = 1.24). In other cohorts of infertile women, only two (8), four (7), 12 (9, 10), and 21 (5, 6) uterine cancers were reported. The largest known previous study with 21 cancer cases and more than 20 years of follow-up reported a nonsignificant association with infertility treatment (5, 6), whereas smaller studies failed to find an excess. The standardized incidence ratio for uterine cancer in the cohort of infertile Israeli women was higher among women treated with ovulation-induction drugs (SIR = 6.8, 95 percent CI: 3.6, 11.5) than among untreated women (SIR = 3.3, 95 percent CI: 1.4, 6.6) (5).

In our cohort of infertile women, clomiphene increased uterine cancer risk (RR = 1.79, $p = 0.09$), with the highest risk found for women who used clomiphene for six or more menstrual cycles (RR = 2.16, $p_{trend} = 0.06$) and who first used clomiphene 20 or more years ago (RR = 2.50, $p_{trend} = 0.04$). The significant latency effect suggests that clomiphene may be an initiator of carcinogenesis and is consistent with the fact that uterine carcinomas are generally slow-growing tumors. Long latency may explain in part why studies that included fewer than 10 years of follow-up failed to find an association between clomiphene use and uterine cancer (7–10), underscoring the importance of long-term follow-up of infertility cohorts.

The relation between clomiphene use and uterine cancer was independent of other predictors of risk. Anovulatory disorders, for which clomiphene is generally the first line of treatment, were associated with a slight increase in uterine cancer risk in our study (RR = 1.39) and in other studies (14); however, adjustment for anovulatory disorders in multivariate models did not appreciably change the estimates of uterine cancer risk associated with clomiphene use in our cohort.

We found that uterine cancer risk associated with clomiphene use was strongest among obese (RR = 6.02) and nulligravid (RR = 3.49) women, with risk estimates particularly elevated for women who were both obese and nulligravid (RR = 12.52). These finding were based on small numbers but were similar after adjustment for other predictors of risk. It is plausible that higher estrogen levels found in obese (15) and nulligravid (16) women act synergistically with clomiphene to increase uterine cancer risk (17, 18). However, we cannot entirely exclude the possibility that, in these subgroups, women who used clomiphene had more severe underlying disease for which we were unable to account.

Clomiphene, similar to other selective estrogen-receptor modulators, elicits estrogen agonist activity in some tissues and estrogen antagonist activity in others. To induce ovulation, a dose of 50 mg of clomiphene is typically administered daily for 5 days during the follicular phase, but doses of 25–200 mg daily are sometimes used for up to 10 days (19). Clomiphene is frequently prescribed for as long as 12 months and, although the half-life of an oral dose is about 5 days, trace amounts of the drug have been found for up to 6 weeks after dosing (19, 20). Its primary mode of action in the treatment of infertility is antagonistic and involves occupying the estrogen-receptor binding sites on the hypothalamic-pituitary axis and preventing the negative feedback effect of estradiol, thereby increasing the number of maturing follicles and, thereafter, plasma estrogen (21).

High levels of unopposed estrogen have been definitively linked to uterine cancer (13). It is therefore likely that clomiphene increases uterine cancer risk simply by indirectly increasing estrogen levels during the first half of the menstrual cycle. However, any strategy used to induce multiple follicular growth will produce supraphysiologic levels of estradiol during the follicular phase, suggesting that all ovulation-stimulating drugs may increase uterine cancer risk. Whether infertility drugs other than clomiphene increase uterine cancer risk requires further investigation. The current study with only three exposed cases did not show an increased uterine cancer risk with gonadotropin use (RR = 0.70).

Clomiphene may also impact uterine cancer risk by interacting directly with estrogen receptors. The effects of clomiphene on the uterus appear complex and have been studied primarily in the context of receptivity of the uterus to embryo implantation (19). Reductions in cervical mucus and uterine thickness among infertile women treated with clomiphene (22) suggest that it acts as an estrogen antagonist in the uterus. However, these studies have been small, observational, and complicated by including women with multiple causes of infertility. In contrast, studies of healthy women with normal menstrual cycles (23, 24), including one randomized clinical trial (24), found that the ultrasonographic appearance and thickness of the endometrium were similar for clomiphene-treated and -untreated cycles.

Although administered differently, clomiphene and tamoxifen appear to share many pharmacologic and toxicologic properties. In addition to having a similar chemical structure, triphenylethylene, these compounds have the same half-life in plasma, are metabolized by the cytochrome P-450 pathway, and are excreted in feces (19). Like tamoxifen, clomiphene exhibits estrogen-agonist effects in the uterus of ovariectomized rats (25, 26) as well as in Ishikawa human uterine adenocarcinoma cells, a well-characterized model for actions of estrogen in the uterus (27). More investigations using in vitro cell models and animal models of carcinogenesis are necessary to more definitively determine whether clomiphene acts as an estrogen agonist or antagonist in the endometrium.

Although our study had a number of strengths, there were some notable limitations. Even though the number of uterine cancers was larger than that in previously published studies, the total number was still small ($N = 39$). Furthermore, given the retrospective nature of the study, we were unable to locate 20 percent of the study population, and 11 percent did not agree to release of their medical records. Additionally, 41 percent of located subjects did not complete a questionnaire, potentially leading to a variety of selection biases that may have affected our results. However, we were unable to detect any systematic biases in the analyses undertaken to assess relations according to source

of subject inclusion or loss. Furthermore, information on ovulation-stimulating drugs, although more complete than in most studies, was still less than optimal. Although information about later drug use was obtained via questionnaire, we could not account for drugs subsequently prescribed by other providers to women who did not complete the questionnaire. Finally, the pattern and dose of drug exposures for many women that we evaluated were quite different from those in current use. However, many of the women in our study received prolonged cycles and very high doses of clomiphene, and many subsequently underwent assisted reproductive technology procedures.

In summary, our study is the first known to suggest that clomiphene increases uterine cancer risk and to demonstrate evidence of both a dose-response and latency effect. Clomiphene did not increase either ovarian or breast cancer risk in this cohort; however, we observed slight elevations in risk for both cancers among women followed for more than 20 years (28, 29). Although these findings need to be confirmed by other epidemiologic studies and better supported by toxicologic investigations, our study has a number of strengths over previous investigations. In addition to having the longest follow-up and the most uterine cancers diagnosed (albeit only 39), our study collected detailed information on drug use, underlying causes of infertility, and other important risk factors obtained through medical record abstraction and administration of a detailed questionnaire.

Clomiphene was approved for clinical use in the United States in 1967 (21) and is now one of the most widely used drugs in the management of infertility (19). By 2025, between 5.4 and 7.7 million US women are projected to seek treatment for infertility annually (30). It is therefore of mounting public health importance to clarify the relation between clomiphene use and uterine cancer. Fortunately, uterine cancer is often diagnosed at early stages because of symptoms and has good survival rates (31). It is nonetheless essential to identify subgroups of infertile women, such as those who remain unable to conceive, who may require more intensive monitoring for uterine abnormalities as they enter the postmenopausal years.

ACKNOWLEDGMENTS

National Cancer Institute intramural funding was provided by the US Government.

REFERENCES

1. Grady D, Gebretsadik T, Kerlikowske K, et al. Hormone replacement therapy and uterine cancer risk: a meta-analysis. Obstet Gynecol 1995;85:304–13.
2. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351:1451–67.
3. Kedar RP, Bourne TH, Powles TJ, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. Lancet 1994;343:1318–21.
4. Fishel S, Jackson P. Follicular stimulation for high tech pregnancies: are we playing it safe? BMJ 1989;299:309–11.
5. Modan B, Ron E, Lerner-Geva L, et al. Cancer incidence in a cohort of infertile women. Am J Epidemiol 1998;147:1038–42.
6. Ron E, Lunenfeld B, Menczer J, et al. Cancer incidence in a cohort of infertile women. Am J Epidemiol 1987;125:780–90.
7. Doyle P, Maconochie N, Beral V, et al. Cancer incidence following treatment for infertility at a clinic in the UK. Hum Reprod 2002;17:2209–13.
8. Potashnik G, Lerner-Geva L, Genkin L, et al. Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. Fertil Steril 1999;71:853–9.
9. Venn A, Watson L, Lumley J, et al. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. Lancet 1995;346:995–1000.
10. Venn A, Watson L, Bruinsma F, et al. Risk of cancer after use of fertility drugs with in-vitro fertilisation. Lancet 1999;354:1586–90.
11. Brinton LA, Lamb EJ, Moghissi KS, et al. Ovarian cancer risk associated with varying causes of infertility. Fertil Steril 2004;82:405–14.
12. Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol 2. The design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987. (IARC scientific publication no. 82).
13. Rose PG. Uterine carcinoma. N Engl J Med 1996;335:640–9.
14. Klip H, Burger CW, Kenemans P, et al. Cancer risk associated with subfertility and ovulation induction: a review. Cancer Causes Control 2000;11:319–44.
15. Madigan MP, Troisi R, Potischman N, et al. Serum hormone levels in relation to reproductive and lifestyle factors in postmenopausal women (United States). Cancer Causes Control 1998;9:199–207.
16. Bernstein L, Pike MC, Ross RK, et al. Estrogen and sex hormone-binding globulin levels in nulliparous and parous women. J Natl Cancer Inst 1985;74:741–5.
17. Rubin GL, Peterson HB, Lee NC, et al. Estrogen replacement therapy and the risk of uterine cancer: remaining controversies. Am J Obstet Gynecol 1990;162:148–54.
18. Shields TS, Weiss NS, Voigt LF, et al. The additional risk of uterine cancer associated with unopposed estrogen use in women with other risk factors. Epidemiology 1999;10:733–8.
19. Goldstein SR, Siddhanti S, Ciaccia AV, et al. A pharmacological review of selective oestrogen receptor modulators. Hum Reprod Update 2000;6:212–24.
20. Mikkelson TJ, Kroboth PD, Cameron WJ, et al. Single-dose pharmacokinetics of clomiphene citrate in normal volunteers. Fertil Steril 1986;46:392–6.
21. Nasseri S, Ledger WL. Clomiphene citrate in the twenty-first century. Hum Fertil (Camb) 2001;4:145–51.
22. Nakamura Y, Ono M, Yoshida Y, et al. Effects of clomiphene citrate on the uterine thickness and echogenic pattern of the endometrium. Fertil Steril 1997;67:256–60.
23. Sereepapong W, Suwajanakorn S, Triratanachat S, et al. Effects of clomiphene citrate on the endometrium of regularly cycling women. Fertil Steril 2000;73:287–91.
24. Triwitayakorn A, Suwajanakorn S, Triratanachat S, et al. Effects of initiation day of clomiphene citrate on the endometrium of women with regular menstrual cycles. Fertil Steril 2002;78:102–7.
25. Young RL, Goldzieher JW, Chakraborty PK, et al. Qualitative differences in estrogenic/antiestrogenic effects of clomiphene and zuclomiphene. Int J Fertil 1991;36:291–5.

26. Sato M, Rippy MK, Bryant HU. Raloxifene, tamoxifen, nafoxidine, or estrogen effects on reproductive and nonreproductive tissues in ovariectomized rats. FASEB J 1996;10:905–12.
27. Bramlett KS, Burris TP. Target specificity of selective estrogen receptor modulators within human uterine cancer cells. J Steroid Biochem Mol Biol 2003;86:27–34.
28. Brinton LA, Lamb EJ, Moghissi KS, et al. Ovarian cancer risk after use of ovulation-stimulating drugs. Obstet Gynecol 2004;103:1194–203.
29. Brinton LA, Scoccia B, Moghissi KS, et al. Breast cancer risk associated with ovulation-stimulating drugs. Human Reprod 2004;19:2005–13.
30. Stephen EH, Chandra A. Updated projections of infertility in the United States: 1995–2025. Fertil Steril 1998;70: 30–4.
31. Chen LM, McGonigle KF, Berek JS. Uterine cancer: recent developments in evaluation and treatment. Oncology (Huntingt) 1999;13:1665–70.